EXHIBIT 50
FILED UNDER SEAL

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD.,	)	
Plaintiff,	)	
v.	)	
SAREPTA THERAPEUTICS, INC.,	)	
Defendant.	)	**C.A. No. 21-1015-GBW**
SAREPTA THERAPEUTICS, INC.,	)	
Defendant/Counter-Plaintiff,	)	
v.	)	
NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC.	)	
Plaintiff and Counter-Defendants.	)	

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Wilmington, Delaware
Wednesday, May 3, 2023
Markman Transcript

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BEFORE: HONORABLE GREGORY B. WILLIAMS
UNITED STATES DISTRICT COURT JUDGE

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Michele L. Rolfe, RPR, CRR

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PROCEEDINGS

(REPORTER'S NOTE: The following Markman was held in Courtroom 6B, beginning at 10:00 a.m.)

THE COURT: Good morning. You may be seated. All right. Let's start by having counsel put appearances on the record.

MS. DUDASH: Good morning, Your Honor. Amy Dudash from Morgan Lewis for plaintiff, Nippon Shinyaku. And with me here today is Amanda Williamson, Michael Sikera, Eric Kraeutler, Zachary Miller, Krista Venegas, as well as our client representative patent attorney from Nippon Shinyaku.

THE COURT: Good morning, all.

MS. DELLINGER: Good morning, Your Honor. Megan Dellinger of Morris Nichols of behalf of Sarepta and the University of Western Australia. And I'm joined this morning by my co-counsel from Finnegan Henderson, William Raich and Yoonjin Lee. And we also have with us this morning Mr. Mark Evans, who is in-house counsel at Sarepta.

THE COURT: All right. So we have a number of terms to construe today and we have two sets of briefs on the issues. We have -- we set aside three hours for this hearing. We'll start with the Wilton patents, so we'll start.

MR. RAICH: Thank you, Your Honor. We have printouts of our demonstratives, may we approach to deliver them?

THE COURT: Yes.

MR. RAICH: And, Your Honor, just by way of background, we've agreed to go term by term, so that's what we intend to do, unless you'd like something different.

THE COURT: No, term by term is typically how we do it.

MR. RAICH: Very good. Thank you. Bill Raich from Finnegan on behalf of defendant and counter-plaintiff Sarepta Therapeutics and The University of Western Australia.

So the Wilton patents disclose the pioneering work of Steve Wilton and colleagues at The University of Western Australia. It disclosed the first ever approved treatment for DMD and covered the first two FDA-approved treatments targeting exon 53. Sarepta's VYONDIS product, approved in 2019. And Nippon Shinyaku's VILTEPSO product approved the following year.

There are, as you know, three terms in dispute, shown with yellow, purple, and green highlighting on slide 3. And Nippon Shinyaku has identified three subterms that it believes should be separately construed.

And the disputed phrases work in unison to

structurally describe the claimed antisense oligonucleotide, thus construing them in the context of the claimed invention as a whole just makes sense.

That's also consistent with the Federal Circuit's guiding principal, the context of the surrounding words of the claim must be considered.

Indeed, Nippon Shinyaku understood how to read these terms in context. As mentioned, they have a product on the market that, just like Sarepta's, is directed to a target region of exon 53 of the human dystrophin pre-mRNA, and has all Ts, or thymines, instead of Us, or uracils.

And what you will see, Your Honor, is that by extracting terming that describe the claimed antisense oligonucleotide from the surrounding claim language, Nippon Shinyaku's constructions either impermissibly broaden the claims, as in the term "a base sequence," or make no sense, as in the context "annealling site." And as the Federal Circuit said, that's why Nippon Shinyaku's approach leads their constructions astray.

Now, Nippon Shinyaku asserts that five separate terms are indefinite. But NS has a high burden; it needs to prove indefiniteness by clear and convincing evidence.

It's also premature to evaluate indefiniteness, Your Honor. As courts in this circuit routinely refrain from reaching indefiniteness at this early stage of the

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all and antecedents that come before the clause, including the claimed antisense oligonucleotide, as in *Finisar*.

And the specification also supports Sarepta's construction. The specification lists oligonucleotides, and those oligonucleotides are always shown with one type of base, not mixtures of Us and Ts, but, for example, Us. And it also states that the U bases may be shown as Ts for morpholinos, which is what's claimed here. And NS acknowledges that the examples in the UWA patent lists oligonucleotides but only uracil bases not a mixture.

Now, the prosecution history confirms Sarepta's proposed construction. So this is a parent application that had parallel language. And the applicant's statements during prosecution are as follows: "The pending claims are drawn to antisense oligonucleotides having the following elements" -- and there's a number of listed of elements, and number three is uracil bases or thymine bases. So the antisense oligonucleotide having uracil bases are thymine bases.

Later in prosecution, in discussing generating an antisense oligonucleotide, and the context of the prior art, applicant explained, there is no teaching or suggestion to generate an antisense oligonucleotide of 25 bases wherein uracil bases are thymine bases.

So, again, the prosecution history indicates

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that the uracil bases -- or thymine bases clause refers to the antisense oligonucleotide as a whole.

Sarepta's construction is also consistent with general practice in the field. So as Sarepta's expert explained, the use of uracil bases or thymine bases, but not both, is consistent with how antisense oligonucleotides were typically made in the art.

And NS's expert, Dr. Hastings, acknowledged that in many cases oligonucleotides use only thymine or uracil bases, not both.

And NS and Dr. Hastings identified no prior art antisense oligonucleotide containing both uracil and thymine bases, nothing in the prior art. And if you look at products, if you look at Golodirsen and Viltolarsen, you can see that they have thymines throughout, not mixtures of Us and Ts.

Now, this shows NS's reformatting of the claims, and what they've done is they've treated the thymine bases phrase differently than the other clauses. So instead of separating out every clause that has commas, like what Sarepta did, NS has stuck these two clauses together.

And what they are suggesting is that an alternative reading is that the uracil bases are thymine bases modifies just this portion of the claim and not the antisense oligonucleotide as a whole.

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There are multiple reasons why NS's formatting of Claim 1 is inconsistent with the claim's plain language. First of all, there are serial commas and they signify that each element set off by a comma is an additional limitation.

Secondly, the term "in which" is a synonym for the term "wherein," they mean the same thing. In fact, as I just showed you, they were used interchangeably during prosecution.

And, third, had the thymine bases phrase been good modifying SEQ ID NO: 195 only, there would have been no reason to have a comma between the two phrases, wouldn't need that common if it was intended to just modify the SEQ ID NO: 195.

Now, NS's arguments regarding the other intrinsic evidence are flawed. So in their responsive claim construction brief, that is how they attempt to address the prosecution. They explain that the listed elements in the list from prosecution don't have a parallel structure that is typical of ordered lists of items.

But let's look at the excerpt from the prosecution. It's an antisense oligonucleotide having the following elements, one, two, three, four, five, and six. That is a parallel structure typical of ordered lists of items. And, in fact, number three is that uracil bases are thymine bases for the antisense oligonucleotide.

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Similarly, and this was the second box on slide 46, it's the antisense oligonucleotide, wherein it comprises 20 consecutive bases and wherein uracil bases are thymine bases and wherein. Again, this is a parallel structure typical of an ordered list of items.

Now, NS also argues in their claim construction brief that the specification of the UWA patents teaches that base substitutions can be made at individual bases in an oligonucleotide, confirming that oligonucleotides can have mixtures of thymines and uracil bases.

But, again, first of all, the mere fact that there is an alternative embodiment disclosed in the asserted patent is not encompassed -- that is not encompassed by our claim construction, does not outweigh the language of the claim, especially when the Court's construction is supported by intrinsic evidence. And, respectfully, that's exactly the case here, the language of the claim and the intrinsic evidence support Sarepta's proposed construction.

Further, respectfully, this discussion, I think, is not in any way clear that it's discussing substituting uracil for thymines. I think they are misinterpreting the specification, even beyond the legal point.

So, a skilled artisan, if you choose to construe this term, would choose Sarepta's construction, which is appropriate in view of the grammar and syntax of the claims,

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the specification's exemplary embodiments, the prosecution history, which lists uracil bases as thymine bases as a characteristic of the antisense oligonucleotide, and general practice in the art.

THE COURT: Okay.

MR. RAICH: Thank you, Your Honor.

MR. KRAEUTLER: Good morning, Your Honor. Eric Kraeutler for Nippon Shinyaku.

THE COURT: Good morning.

Mr. Kraeutler, let me start by asking you this: Is NS able to point to any prior art where there's antisense oligonucleotide that contains both uracil and thymine bases?

MR. KRAEUTLER: Yes, Your Honor. Our expert, Dr. Hastings, pointed to a number of examples, but let me focus on one.

And if we could bring up slide 82, please.

This is the '601 patent, which is in the prior art. This patent involved different inventors to another patent, but also directed to a oligomers capable of causing exon skipping.

The '601 patent -- if we can go to the next slide -- claimed that an oligomer comprising a sequence of one of three listed sequences where X in the sequence is defined to be uracil or thymine.

And if we could go to the next slide, the '601

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specification explained that the base sequence of the molecules could contain all thymines or all uracils or a combination of the two.

So that is an example of -- from the prior art. There are other examples in Dr. Hastings' declaration. And, Your Honor, there is nothing that says that scientifically, chemically, one cannot have uracils and thymines in the same oligonucleotide.

THE COURT: All right.

MR. KRAEUTLER: If we could return to slide 65, please. So the issue, Your Honor, is indefiniteness, the parties agree that the phrase at issue modifies a sequence of nucleobases. And the question is whether a person of ordinary skill in the art could determine which of two possible sequences.

Next.

This is the language of Claim 1 from the '851 patent with the disputed language underlined. Similar language appears in all of the asserted Sarepta patents.

Next.

And this is what creates the ambiguity. The disputed modifier is proceeded by recitation of two different sequences. There is the longer sequence of the entire antisense oligonucleotide, that is the sequence of 20 to 31 bases.

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And there is the shorter sequence that is derived from SEQ ID 195. That's a sequence of at least 12 bases, and it could be as few as 12 bases.

Next.

So the disputed language concerns the substitution of thymine bases for uracil bases. There's already been a fair amount of discussion on that, Your Honor. But what I'd like to point out is these are the five bases that are found in nature in DNA or RNA. Uracil and thymine have very similar chemical structures. In nature, uracil is found in -- in RNA and thymine is found in DNA. They both pair with adenine, which is found in both DNA and RNA.

Next.

So Sarepta's proposed construction is shown on the left. And actually all through their presentations today, they've shown the claim formatted in this manner.

James, could you go back to 66?

But that's how the claim appears in the patent. So the formatting has been added.

Let's go back to 69.

But Sarepta's -- supports its construction with this formatting. And their proposed construction, we believe, is plausible, and there's some support for it, as they have argued. But the reformatting on the right is more

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logical.

The opening phrase shown in blue describes the entire oligonucleotide. The phrases that modify the entire oligonucleotide all begin with the words "wherein," and all of them recite the antecedent subject. The phrase at issue begins with a different conjunction; it begins with the words "in which," it does not identify an antecedent subject. And that is because it immediately follows a listing of the bases of SEQ ID 195 which includes 10 uracils.

So when it says "in which uracil bases are thymine bases," the logical reading is it refers back to that list that immediately proceeds it.

THE COURT: But doesn't that -- isn't that contrary to the structure of the separate commas? You know, why would you only have -- all of them are separated by commas, why would you only take that phrase and have it modify the preceding phrase and not do that for all of them?

MR. KRAEUTLER: So, Your Honor, we agree that the use of commas can be a tool used to construe the grammar or syntax, but it's only one tool, it's only one indication. And here, the inventors chose a different conjunction for this phrase as opposed to all the others, and the inventors chose -- did not identify an antecedent's subject; although, the phrase immediately follows a listing that included

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uracil bases.

So too much weight is being put on the comma by Sarepta. There are other grammatical and syntax indicators here that we think should be given at least as much weight. And that's the reason why we have indefiniteness.

THE COURT: Okay. I understand what you're arguing.

MR. KRAEUTLER: So, Your Honor, the more logical interpretation, if we could go to the next slide, is that the first wherein clause should be read together with the in which clause, and this is the result. It was a way of reciting a sequence that has Cs and Ts and Gs and As that was derived from SEQ ID NO. 195, but is different from it.

This is exactly what's shown in the specification.

Next.

The uracil bases of SEQ ID NO. 195 can be thymine bases. That's in the specification. The UWA -- next, please. The UWA specification also does not support Sarepta's construction. There's no antecedent subjects to be modified by the phrase "when uracil bases are thymine bases." Nowhere does the specification say that the entire oligonucleotide contains only uracil bases or only thymine bases.

So there's no context for the phrase "uracil

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bases are thymine bases" in relation to the base sequence of the entire oligonucleotide.

And just as important, the UWA patents teach that substitutions or modifications, like substituting uracil for thymine or thymine for uracil, can be performed on a nucleotide by nucleotide bases, as shown in the excerpts on this slide 74.

Next.

In her declaration, Professor Hastings provides a number of examples of sequences of 20 to 31 bases for the entire oligonucleotide, that include 12 bases of SEQ ID NO. 195 in which the uracil bases of SEQ ID 195 are thymine bases.

And these examples, Your Honor, would infringe under what I described as the more logical interpretation of the text, but would not infringe under Sarepta's interpret.

Sarepta -- next, please -- relies on statements made by the UWA applications in response to a Section 103 rejection during prosecution. This was prosecution of a different patent application involving related claims. But as I'll show in the next slide, those claims were similar in grammatical structure to the claims at issue, but they involved a different sequence, SEQ ID NO. 193.

In that -- in that rejection during prosecution, in response to that rejection, the UWA applicants argued --

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next -- that none of the prior art references cited by the Patent Office teach or suggest all of the elements of the claimed invention. And, among other things, they said, those references said nothing about substituting thymine for uracil in any part of the oligonucleotide.

So -- so they argued that there was no teaching of substitution, not in the longer sequence of the oligonucleotide and not in the shorter specific sequence of SEQ ID 193.

So the distinction at issue in this hearing was completely unimportant in that portion of the prosecution. In fact, the distinction probably wasn't recognized by the UWA applicants at all. Their point was that the prior art doesn't teach any substitutions.

Next.

So Sarepta relies on two passages from the UWA inventors' response. In this passage, the UWA applicants paraphrased the claim, but they omitted all of the conjunctions, including all of the whereins and including the in which. And they omitted the listing of the specific bases that made up SEQ ID 193.

But that doesn't change the fact that at least ten uracil bases included in that sequence were at least equally as plausible as the antecedent subject for the phrase "uracil bases or thymine bases."

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Next.

In the second passage, the UWA applicants again paraphrased the claim, but this time they used the conjunction wherein for all of the claims elements.

And, frankly, Your Honor, this is no more significant than having a conjunct -- having no conjunction for any of the elements in their other paraphrase. It doesn't change the fact that the clause still doesn't begin with an antecedent subject; it doesn't change the fact that it still immediately follows a reference to a sequence that had ten uracil bases in that case as well as the sequence in our case.

So, finally, this paraphrase is no more indicative or probative of the inventors' intent that the actual claim language in this case, in which different conjunctions were used, in which the antecedent subject was recited every time the inventors meant the entire antisense oligonucleotide, and did not do so for the phrase at issue.

Thank you, Your Honor.

THE COURT: All right. Thank you.

MR. RAICH: Your Honor, just very briefly, a couple of points that I'd like to make about counsel's comments.

Counsel referred to the '601 patent and characterized it as prior art. And on their slide they

deprotecting agent. But, again, nothing in the claims or the specifications suggest that such indirect reactions are allowed, either under the plain claim language or the sole embodiment disclosed in the specification.

NS's counsel argue that somehow it is wrong that Sarepta's construction read out this method B. But respectfully, there's nothing that the come -- that NS's claim cannot cover method B under Sarepta's constructions. The claim says what it says, and the claims as written should be construed, as the Federal Circuit explained in the *Chef America*.

And for those reasons, Sarepta's construction should be adopted because it is based on the plain claim language and is also consistent with the intrinsic evidence, including the sole embodiment in the specification, and that's how the skilled artisan would have understood, as explained by Dr. Pentelute.

THE COURT: All right. I understand your argument.

MR. MILLER: Just a few very quick points, Your Honor. First, my opposing counsel mentioned the fact that the claims have lettered steps and numbered compounds, and argued that those letters and numbers imported a -- implied a step order.

Your Honor, respectively, those letters and

numbers are used for organizational purposes, so that in later dependent steps, instead of reciting the entire step, the dependent claim -- I'm sorry, in dependent claims, instead of reciting an entire step from the independent claim, the independent claim can simply identify step E as the one being further modified, or other steps like that.

And the same reason those numbered compounds are provided numbers, so you can use a shorthand instead of repeating the structure of each numbered compound every single time it's used, you can just recite to the earlier numbered structure.

I'd also like to pull up slide 21 from my opposing counsel's presentation. And I think this generally shows the improper way that -- that Sarepta has construed these claims. Sarepta is -- if you look at the claims themselves, they say "reacting said Compound 3. And reacting said Compound 4."

Instead of looking at that claim language, Sarepta is importing the underlined limitations from the specification, from an embodiment in the specification that Compound 3 must be produced in step B or produced in step C into the claims themselves.

And we already know that importing limitations from the specification, from an embodiment in the specification, even if it is the only embodiment in the

specification, that's improper. And for those reasons, NS's proposed construction should be adopted, Your Honor.

THE COURT: All right.

MR. MILLER: Thank you.

THE COURT: Thank you.

All right. The Court wants to thank counsel on both sides for your presentations today. The Court will take these matters under advisement and issue a *Markman* ruling as soon as it can. We've been trying to get them out within 60 days, so we will do our best in keep that up.

So with that, that's all I had on the agenda for the day for these parties, so with that we are adjourned.

(Whereupon, the following proceeding concluded at 1:13 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Michele L. Rolfe, RPR, CRR

U.S. District Court